Prior to responding to the specific rejections and discussing the amendments to the claims, a review of the subject invention is deemed appropriate. Within the last decade, enormous advances have occurred in the field of immunology, greatly increasing our understanding of immunoglobulin structure. These advances have also given insight into the function of various portions of immunoglobulins, as well as their overall role in the immune response. Moreover, the advent of monoclonal antibody technology has provided means for producing higher quantities of immunoglobulins specific for predetermined epitopic sites. The more recent development of human monoclonal antibodies has further increased interest in the use of immunoglobulins for therapeutic purposes.

As noted in the specification, however, full sized immunoglobulins have certain disadvantages when used in either animal diagnosis or therapy. For example, their size renders them immunogenic when placed in a host, particularly when the immunoglobulins are conjugated to tracers, enzymes, or other materials. Further, their large size causes relatively rapid clearance from the blood stream of the host.

Traditional manipulation of immunoglobulins, such as by enzyme cleavage, has been performed for many years, but producing such fragments is extremely difficult and time-consuming. Moreover, the manipulations often result in the presence of extraneous materials that are very difficult to remove by standard purification techniques. This increased impurity level often renders these preparations unsuitable for therapeutic purposes. The present invention

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not only overcomes these difficulties, but provides significant advantages over other known preparations of immunoglobulins or fragments thereof.

The novel protein complexes of the present invention are comprised of homogeneous compositions made up of the variable regions of the light and heavy chains of an immunoglobulin. These chains form a specific binding complex ("rFv") reactive with a predetermined haptenic or determinant site. The rFv complexes are produced by introducing cDNA encoding for the variable regions of light and heavy chains into an appropriate expression vector for transcription and translation in a chosen host. The resulting truncated light and heavy chains can combine to form the rFv complex, which exhibits a high affinity for a predetermined epitope.

The relatively small size of the rFv complexes makes them extremely useful for diagnostic and therapeutic studies. As detailed on page 4, line 2ff of the specification, the rFv complex will generally have polypeptide chains of fewer than about 125 amino acids, but normally greater than about 60 amino acids, much less than full size immunoglobulins.

By manufacturing the rFv complexes in this manner, one can readily modify the binding specificity of the complex through well-known recombinant DNA techniques. Moreover, bulk quantities of these smaller proteins can be produced in any of a wide variety of hosts, reducing the cost of making the compounds, as well as the expense of their subsequent purification.

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Returning now to the rejections, it can be seen that the specification provides those skilled in the art with the means to make and use the compositions of the present invention. The rejection under 35 U.S.C. 101 is respectfully traversed.

Beginning at page 5 of the specification and continuing through page 18, the applicants have provided significant details as to the preparation of the rFv compositions, including: 1) isolation of relevant DNA sequences; 2) introduction of the DNA sequences coding for the polypeptides of interest into an appropriate expression vector; and 3) expression and isolation of the light and heavy chain variable regions to form the desired rFv compositions. Thereafter, in the specification beginning at page 9 and continuing for 24 pages up to page 43, applicants have provided an example of the present invention utilizing an rFv composition reactive with dinitrophenyl. The specifics of the experimental procedures have been provided in painstaking detail, including buffer systems, reaction times, sequence data and the like.

As further evidence of the operativeness of the present invention, applicants enclose with this Response the following two recent publications describing the production of functional antibodies using recombinant DNA techniques:

Exhibit A - "The Synthesis and In Vivo Assembly of Functional Antibodies in Yeast", Wood, C. et al., Nature 314:446-449 (1985); and

Exhibit B - "Assembly of Functional Antibodies from Immunoglobulin Heavy and Light Chains Synthesised in E.

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coli", Boss, M. et al., Nucleic Acids Research 12:3791-3806 (1984).

Based on these references, there can be little doubt of the operability of the present invention, and the rejection under 35 U.S.C. 101 should be withdrawn.

All of the claims were rejected under 35 U.S.C. 112, first and second paragraphs. The rejection of the first paragraph is respectfully traversed, whereas the amendments to the claims overcome the rejections under the second paragraph.

Claim 20 has been amended in accordance with the Examiner's suggestions. First, the term "translation" has been replaced with the term "expression" to more accurately reflect the progression from a DNA sequence into its encoded polypeptide. Further, to avoid possible ambiguities, Claim 20 has also been amended to clarify that the expression of the DNA sequence coding for the variable region occurs in the absence of expression of its natively associated constant region DNA sequence. Finally, Claim 22 has been amended to conform with the Examiner's proposal by deleting the reference to "a domain."

With respect to the breadth rejection, applicants respectfully submit that the disclosure in the specification is enabling for the claims as amended. Applicants are certainly aware of M.P.E.P. section 706.03(n) and section 706.03(z). Also, applicants do not dispute that the mammalian immune system is unique in certain aspects, e.g., the number of different protein compounds produced having extremely high specificities for various molecular structures. However, none of this should limit the scope of the

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present invention, which provides a mean for producing binding compositions based on the variable region of any type of immunoglobulin. Whether from mammals or other animals, the same procedures described in the subject specification may be readily utilized to produce the claimed binding compositions. Accordingly, the rejection under 35 U.S.C. 112, first paragraph, as well as under the second paragraph thereof, should be withdrawn.

In addition to the formal rejections, Claims 20-25 were rejected under 35 U.S.C. 102(b) as being anticipated by Sharon et al., Rosemblatt et al. or Pawlowski et al. Similarly, the claims are rejected under 35 U.S.C. 102(b) or (e) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over the Ehrlich et al. or Auditore-Hargreaves patents. These rejections are respectfully traversed.

Considering first the two cited patents, it can be seen that neither can be used as a reference under 35 U.S.C. 102(b), because the patents did not issue until after the filing date of the parent application of the subject application. In fact, the Auditore-Hargreaves patent also cannot be used as a reference under either 102(e) or 103, given a filing date of October 4, 1983, or at best the May 5, 1982 date of its parent divisional application.

Considering the Ehrlich et al. reference with the three additional cited publications, it can readily be seen that none in any way anticipate the present invention as claimed. While all of the references are directed toward immunoglobulins or fragments thereof, within their four corners no reference discloses the claimed rFv complex. For

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example, none of the references describes the polypeptide chains being produced by the expression of a DNA sequence coding for the variable region, when expression of the naturally associated constant region DNA sequence is absent. Moreover, the rFv would not be identical to the compositions described in the references. For example, the glycosylation patterns would differ greatly. The claimed composition did not exist prior to the present invention, and certainly none of the cited references disclose it.

Claims 20-25 were further rejected under 35 U.S.C. 103 as being unpatentable over Zakut et al., Seidman et al. or Early et al. (Cell), in view of Amster et al. Also, all of the claims were rejected under 35 U.S.C. 103 as being unpatentable over these same references, and further in view of statements at page 40 of the specification or in view of Ptashne et al. These rejections are respectfully traversed.

Applicants do not dispute that the sequences disclosed in the subject specification are derived from Seidman et al. and Early et al., nor that Amster et al. suggests the possibility of synthesizing specific antibody molecules in bacteria. Applicants contend, however, that such disclosures do not render the present invention obvious.

First, Amster et al. teach the synthesis of a portion of the variable region of an IgG molecule in conjunction with the associated constant region. Moreover, the immunoglobulin pieces synthesized are part of a fusion protein, with the additional portion being supplied by the β-lactamase peptide coding region. Thus, this reference is inapposite.

The Examiner's reliance on applicants' alleged admitted state of the prior art at page 40 of the specification is not understood. That an expression vehicle exists in the prior art does not render the present invention obvious. Similarly, that Ptashne et al. may teach the expression of foreign genes in bacteria adds nothing of significance to the other references.

All of the cited references merely reiterate the state of the art at the time the present invention was made. None of these references, even when cited in combination, disclose nor render the claimed composition obvious. Indeed, the rFv complex is quite distinguishable over any and all of the cited references. For example, the references are not directed toward portions of the variable region of an immunoglobulin, which has been produced separately from it's constant region.

For the reasons discussed fully above, the present invention provides a substantial improvement over any existing immunoglobulin compositions. In actuality, the cited references teach away from the present invention by their attention to the cloning of entire immunoglobulin genes, i.e., both constant and variable regions. Instead, the applicants recognized and have provided a means for producing a novel composition not even contemplated by others skilled in the art.

It is therefore respectfully submitted that for all of the above reasons, applicants' claims are patentable over the cited references and that the rejection under 35 U.S.C. 103 should be withdrawn. Thus, in view of the above amendments and the additional remarks, the Examiner is

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respectfully requested to allow Claims 20-25, as amended, and pass this application to issue.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (415) 493-2590.

Respectfully submitted,

TOWNSEND and TOWNSEND

Date 9/20/85

By William M. Smith
William M. Smith
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11-JR01:jr/gs

Enclosures
A. "The Synthesis and In Vivo Assembly of Functional Antibodies in Yeast", Wood, C. et al., Nature 314:446-449 (1985)
B. "Assembly of Functional Antibodies from Immunoglobulin Heavy and Light Chains Synthesised in E. coli", Boss, M. et al., Nucleic Acids Research 12:3791-3806 (1984)

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